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# CASE CONFERENCE

## SUCCESSFUL MANAGEMENT OF EXCITED DELIRIUM SYNDROME WITH PREHOSPITAL KETAMINE: TWO CASE EXAMPLES

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### ABSTRACT

Excited delirium syndrome (ExDS) is a medical emergency usually presenting first in the prehospital environment. Untreated ExDS is associated with a high mortality rate and is gaining recognition within organized medicine as an emerging public safety problem. It is highly associated with male gender, middle age, chronic illicit stimulant abuse, and mental illness. Management of ExDS often begins in the field when first responders, law enforcement personnel, and emergency medical services (EMS) personnel respond to requests from witnesses who observe subjects exhibiting bizarre, agitated behavior. Although appropriate prehospital management of subjects with ExDS is still under study, there is increasing awareness of the danger of untreated ExDS, and the danger associated with the need for subject restraint, whether physical or chemical. We describe two ExDS patients who were successfully chemically restrained with ketamine in the prehospital environment, and who had good outcomes without complication. These are among the first case reports in the literature of ExDS survival without complication using this novel prehospital sedation management protocol. This strategy bears further study and surveillance by the prehospital care community for evaluation of side effects and unintended complications. **Key words:** excited

delirium; agitation; ketamine; prehospital; chemical restraint

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### INTRODUCTION

Excited delirium syndrome (ExDS) is a medical emergency characterized by the clinical constellation of profound psychomotor agitation and delirium. As a semantic term, ExDS was first coined in the mid-1980s by Wetli and Fishbain to describe a series of deaths in Florida that were preceded by this clinical behavior.<sup>1</sup> At the time, it was felt to be a behavioral manifestation due to acute cocaine intoxication. Since that time, other writings have connected this syndrome to other illicit intoxicants as well as underlying mental illness.<sup>2,3</sup>

The concept of ExDS is generally defined as a spectrum of clinical behaviors and signs that includes aggressive behavior with an altered sensorium, hyperthermia, exhibition of “superhuman” strength, diaphoresis, and lack of willingness to yield to overwhelming force.<sup>4</sup> Severe ExDS is associated with a high mortality rate and has emerged as a significant public safety problem. The pathophysiology leading to death in ExDS is postulated to be profound metabolic acidosis and unchecked catecholamine surge.<sup>4</sup> This has led some prehospital systems to develop protocols for treatment of suspected ExDS with the goal of interrupting the downward spiral of worsening pathophysiology.<sup>5</sup>

We describe two cases of successful ExDS management without complication utilizing ketamine as a chemical restraint in the prehospital environment. We believe that these cases are among the first description in the medical literature of this novel management strategy describing overall success with no complications. This strategy bears further study and surveillance by the prehospital care community for evaluation of side effects and unintended complications.

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## CASE REPORTS

### Case 1

In January 2012, a 35-year-old, 103-kilogram white man was exhibiting bizarre behavior in an urban alley. He was observed to be shirtless (the environmental temperature was 11°F/−11.7°C) and trying to enter a business that was not open. When confronted by a security officer, he exhibited agitation, vocal perseveration, partial nudity, and incoherence. As the security officer tried to detain him, he became more agitated and violent, prompting a call to 9-1-1 for help. Although this was not known at the time of the 9-1-1 call, he was later noted to have a history of multiple psychiatric and polysubstance abuse problems.

Two law enforcement officers (LEOs) arrived and attempted to control the subject, but were unsuccessful. They later described their attempts as futile and noted that the subject was remarkably strong and did not react to manual pain compliance-control techniques. They requested help, and multiple LEOs responded to assist until there were a total of eight LEOs on the scene struggling with the subject. Emergency medical services (EMS) arrived and described the subject as prone on the ground, with each of the eight LEOs attempting to restrain an extremity, the head, or the buttocks, but instead being easily tossed around despite their advantageous numbers, training, equipment, and positioning. They described the subject as forcefully striking his own head on the pavement while yelling nonsensically. Two LEOs were injured during this process. The LEOs used only manual control techniques (no impact, aerosolized, or conducted-electrical weapons) during their attempts and reported that these techniques were ineffective.

The subject was eventually brought under control with a 500-mg intramuscular (IM) injection of ketamine hydrochloride in the buttocks administered through clothing. The total time from security guard encounter to sedation was reported to be less than 12 minutes. The EMS providers reported excellent sedation within 4 minutes after the ketamine administration. Prehospital vital signs included a pulse rate of 122 beats/min and a respiratory rate of 32 breaths/min. The EMS personnel reported that a full set of vital signs was not obtained because of the combativeness of the subject. He was immediately transported to a nearby tertiary receiving hospital in handcuff restraints in a semiprone/recovery position.

Upon arrival at the hospital emergency department (ED), he was noted to be sedate and unresponsive to verbal or painful stimuli, with the following vital signs: temperature 102.4°F/39.1°C, pulse rate 122 beats/min, respiratory rate 32 breaths/min, blood pressure 128/58 mmHg, and oxygen saturation 100% on room air. He was kept in four-point restraints on ar-

rival as a precaution. The primary survey was notable for rapid, deep, and labored breathing.

Analysis of the subject's blood for standard resuscitation biomarkers was performed on arrival. The following were of interest in this case: arterial pH 7.00, partial pressure of carbon dioxide (pCO<sub>2</sub>) 54 mmHg, and bicarbonate 13 mEq/L; venous potassium 3.4 mEq/L, creatinine 1.9 mg/dL, troponin I qualitatively "normal" (no further testing done), and creatine kinase (CK) 2,562 units/L; urine drug screen was positive for metabolites of cocaine but did not indicate acute cocaine usage. An initial lactate level was not obtained, but when analyzed three hours after admission the level was 0.9 mg/dL.

The patient was endotracheally intubated and placed on a mechanical ventilator because of concern for his significant acidosis. The results of a computed tomographic head scan and a lumbar puncture were both normal. The patient was admitted to the intensive care unit and over the course of the next 72 hours was weaned off of sedation and extubated. With the exception of CK level, which peaked at 3,402 units/L at 48 hours after admission, the patient's serum abnormalities quickly returned to normal. His mental status returned to normal and his psychiatric status was verified to be at baseline by hospital day 3. He did not remember his violent behavior and was amnesic to the restraint and sedation event. He admitted to chronic cocaine abuse but denied recent, acute use surrounding this event. He was discharged from the hospital and lost to follow up after 96 hours with the diagnoses of altered mental status with agitation and combativeness, acidosis, rhabdomyolysis, acute kidney injury, and fever.

### Case 2

In February 2012, a 40-year-old, 80-kilogram African American man was involved in a violent altercation with a woman. Her screams during the assault prompted bystanders to call 9-1-1. Although this was not known at the time of the 9-1-1 call, the subject was later shown to have a history of schizophrenia with paranoid features, chronic cocaine abuse, chronic alcohol abuse, and hepatitis B. Upon the arrival of LEOs, it was noted that the subject was uncooperative, agitated, partially nude (the environmental temperature was 17°F/−8.3°C), and incoherent. He was noted to be screaming numerous requests to speak with God. A request for an EMS response to be present was made at that time. A significant fight with the LEOs ensued, including a brief foot chase for no more than one city block. The subject was eventually brought under control with deployment of a single conducted-electrical weapon (TASER X26 device, TASER International, Inc., Scottsdale, AZ) and then was tackled by several LEOs. EMS was present and chemically sedated him with

375 mg of IM ketamine hydrochloride in the thigh. The time from LEO encounter to sedation was reported to be less than 8 minutes. EMS reported good effect from the sedative in approximately 3 minutes. Prehospital vital signs included a pulse rate of 123 beats/min and a respiratory rate of 42 breaths/min. EMS reported that a full set of vital signs was not obtained because of the combativeness of the subject. He was immediately transported to a nearby tertiary receiving hospital in handcuff restraints in a semiprone/recovery position.

Upon arrival at the ED, he was noted to be sedate and unresponsive to verbal or painful stimuli, with the following vital signs: temperature 101.3°F/38.5°C, pulse rate 168 beats/min, respiratory rate 35 breaths/min, blood pressure 151/69 mmHg, and oxygen saturation 93% on room air. He was placed in four-point restraints on the resuscitation bed as a precautionary measure because statements by the EMS personnel and LEOs present warned of the difficulty in controlling his violent behavior. The primary survey was notable for rapid, deep breathing consistent with and indicative of compensation for severe metabolic acidosis.

Analysis of the subject's blood for standard resuscitation biomarkers was performed on arrival. The following were of interest in this case: arterial pH 6.70, pCO<sub>2</sub> 44 mmHg, and bicarbonate 5 mEq/L (indicating an incomplete respiratory compensation for a severe metabolic acidosis); venous potassium 4.2 mEq/L, creatinine 1.6 mg/dL, lactate 30 mg/dL, troponin I 0.083 ng/mL, and CK 542 units/L; urine drug screen was positive for metabolites of cocaine but did not indicate acute cocaine use.

The patient was nasally intubated and placed on a mechanical ventilator at high minute ventilation in order to more fully compensate for his metabolic acidosis. A repeat arterial blood gas analysis obtained within 30 minutes after intubation showed pH 6.82, pCO<sub>2</sub> 34 mmHg, and bicarbonate 5.4 mEq/L. The patient was admitted to the intensive care unit and over the course of the next 48 hours was weaned off of sedation and extubated. His serum biomarkers returned to normal. The troponin I level peaked at 0.213 ng/mL the following day and then normalized. The patient's mental status returned to normal and his psychiatric status was verified to be at baseline by hospital day 2. He had no recollection of the events leading up to his violent behavior and was amnesic to the restraint and sedation event. He did admit to chronic cocaine abuse, but denied use within the previous week. He was discharged from the hospital after 72 hours and his discharge summary listed numerous discharge diagnoses, including profound metabolic acidosis secondary to agitation and cocaine use in the setting of underlying psychiatric disease.

## DISCUSSION

The primary purpose for this case report is to add support in the medical literature for what we believe is a novel and effective management solution for severe ExDS. Excited delirium syndrome usually presents first in the prehospital environment. There is literature support to suggest that first-responder rescuers are able to recognize the clinical features of ExDS in the field.<sup>6</sup> As ExDS becomes more recognizable to clinicians, we believe that its mortality will fall as a result of earlier recognition and intervention.

Excited delirium syndrome is a term that has been used for decades to describe a behavioral syndrome that was first described by Bell as a psychiatric syndrome of lethal, febrile, manic behavior seen within some institutionalized patients in the mid-1800s.<sup>7</sup> At the time, it was called "Bell's mania." The work by Bell, as well as that by Wetli and Fishbain, describes a series of subjects who exhibited clinical behavior very similar to our two cases but went on to die suddenly and unexpectedly. Since then, others have used different terminology such as "agitated delirium," "cocaine agitation and psychosis," and "delirious mania" to describe what appears to be the same phenomenon. However, there is recent consensus of the term ExDS in the emergency medicine literature.<sup>4</sup>

There is little epidemiologic data about ExDS except that it is highly associated with illicit stimulant use, mental illness, and a gender-specific and age-specific risk, as the overwhelming majority of cases in the literature occur in males with a mean age of 36 years.<sup>2,8-10</sup> The severe agitation of ExDS is not seen routinely in cocaine-overdose deaths. Cocaine and cocaine metabolite levels found in the bodies of patients who died of ExDS do not indicate that death occurs from cocaine overdose and suggests a different mechanism of death and a different syndrome.<sup>4</sup> This is consistent with what occurred in our two cases that showed nonacute cocaine metabolites upon toxicology screening of their urine, but did not reveal evidence of cocaine use within the immediate time frame prior to the onset of bizarre behavior. The behaviors seen in an acute ExDS emergency closely resemble delirious, agitated psychosis, and these behaviors are believed to be mediated by an increase in cerebral extracellular dopamine level.<sup>11</sup> This is thought to occur because of downregulation of dopamine transporter protein that allows excess dopamine to persist in the intracellular space causing behavioral change. Mash et al. have demonstrated a lack of dopamine transporter protein activity in persons exhibiting ExDS behavior at or very close to the time of death that supports this mechanism.<sup>12</sup> There is a high association between late-stage ExDS and death due to cardiopulmonary arrest. It is believed that ExDS occurs along a spectrum, starting initially as

odd behavior that may be dismissed by witnesses if unrecognized. If allowed to continue unchecked, ExDS progresses to severe states of agitation, paranoia, and incoherence.<sup>13</sup> The dangerous pathophysiology associated with this acute emergency is believed to be a rapidly worsening metabolic acidosis in addition to significant catecholamine surge that may induce cardiac dysfunction.<sup>14</sup> Both conditions are associated with fear or paranoia-driven violent acts, fleeing from attempts at help or rescue, and significant physical activity usually in the form of resistance to control and restraints.<sup>15</sup> It is likely that because of incoherence, the ExDS subject does not recognize or correctly interpret the normal internal cues of extreme exhaustion and is able to continue his or her vigorous physical activity unabated. This late-stage ExDS behavior is classic, associated with profound acidosis and death, and has been described very well in the literature.<sup>16</sup> Stimulant intoxication may also contribute to worsening of these conditions.<sup>17,18</sup> Recommended treatment of ExDS, especially in later stages, primarily consists of medications with sedating or dissociative properties.<sup>19</sup>

The use of ketamine as a successful dissociative sedative within the hospital has been described in the literature for conditions requiring deep procedural sedation, with minimal complications.<sup>20,21</sup> Ketamine has also been used on trauma patients for agitation control in the prehospital setting.<sup>22</sup> Additionally, there have been case reports of successful use of ketamine in prehospital novel rescue situations to facilitate chemical restraint and extrication.<sup>23,24</sup>

We would caution against using ketamine sedation in situations that do not warrant the immediate need for interruption of the severe, life-threatening, metabolic acidosis/catecholamine surge crisis seen in late-stage ExDS. Clinicians should always consider the risk-benefit ratio of a possible intervention. In 2012, Burnett et al. described a case report of laryngospasm as a complication of prehospital ketamine administration in an agitated person.<sup>25</sup> Laryngospasm is a known potential side effect of ketamine and can cause airway compromise. Although that person was labeled as an ExDS patient, the details of that case (near normal pulse rate of 101 beats/min in the field with a respiratory rate of 18 breaths/min, normothermia, normal CK level, and a negative toxicology screen) make it unlikely to be late-stage ExDS with an immediate threat to life. Late-stage ExDS, where subjects are wildly agitated and violently exertional, should have marked tachycardia, hyperventilation secondary to metabolic acidosis, and hyperthermia with CK derangement. We would advocate that ketamine not be the chemical solution for every unruly or belligerent subjects, as this would lead to overuse with unnecessary risk.

Ketamine has unique properties that make it well suited for use in the prehospital setting. Typical dosing is 1–2 mg/kg intravenous (IV) and 4–5 mg/kg IM. In the prehospital setting, and particularly in ExDS

where safety of the rescue personnel can be compromised during the struggle for control and restraint, IM administration is the preferred method, as IV access would be difficult to achieve. When given IM, ketamine has an onset of action of approximately 5 minutes and duration of action of 20–30 minutes. These properties are ideal for interrupting and controlling ExDS in the field. Quickly and definitively sedating a patient with ExDS is crucial to stopping the continued catecholamine surge and metabolic acidosis. The side-effect profile for ketamine includes a low risk of laryngospasm, hypersalivation, nausea, and vivid emergence hallucination reactions. This needs to be considered in the overall risk-benefit ratio of need. Our EMS system standing-order protocol reserves the use of ketamine for profound agitation involving imminent risk of injury to patient or provider (Fig. 1).

#### PROFOUND AGITATION

1. If the patient is profoundly agitated with active physical violence to himself/herself or others evident, and usual chemical or physical restraints (section C) may not be appropriate or safely used, consider:
  - a. Ketamine 5 mg/kg IM (If IV already established, may give 2 mg/kg IV/IO).
  - b. **DO NOT** attempt to place an IV in a severely combative patient.
2. If Ketamine is administered, rapidly move the patient to the ambulance and be prepared to provide:
  - a. Respiratory support including suctioning, oxygen, and intubation.
  - b. Monitoring of the airway for laryngospasm (presents as stridor, abrupt cyanosis/hypoxia early in sedation period). If laryngospasm occurs perform the following in sequence until the patient is ventilating, then support as needed:
    - Provide jaw thrust and oxygen.
    - Attempt Bag Valve Mask (BVM) ventilation.
    - Intubate over gum bougie/tracheal tube introducer with appropriate RSI medications as needed (per applicable service protocols). Cords likely to be closed if not paralyzed thus the need for introducer.
  - c. If hypersecretion is present, consider Atropine 0.1–0.3 mg IV/IO or 0.5 mg IM.
  - d. If emergence of hallucinations/agitation after administration of Ketamine, consider Midazolam 2–5 mg IV/IO/IM.
3. Consider IV access once sedation occurs (if no IV access previously established and Ketamine given IM) then administer Normal Saline wide open up to 1 liters.
4. Consider Sodium Bicarbonate 1 amp IV/IO push.
5. Rapid transport at earliest opportunity.

FIGURE 1. Hennepin County Emergency Medical Services (EMS) System Advance Life Support Protocols, 2012 edition, Adult Behavioral Emergency. From: Hennepin County Emergency Medical Services System. Advanced Life Support Protocols, 2012 edition. Adult Behavioral Emergencies Protocol, p 68. Available at: [http://www.hennepin.us/files/HennepinUS/HSPHD/Public%20Health%20Protection/Emergency%20Medical%20Services/EMS-System%20Policies/System\\_Policies-Protocols/ALS%20Protocols-Large-Redacted.pdf](http://www.hennepin.us/files/HennepinUS/HSPHD/Public%20Health%20Protection/Emergency%20Medical%20Services/EMS-System%20Policies/System_Policies-Protocols/ALS%20Protocols-Large-Redacted.pdf). Accessed June 30, 2012. Reprinted with permission from the Hennepin County Human Services and Public Health Department, EMS Planning and Regulation Unit, EMS Advisory Council. IM = intramuscular; IO = intraosseous; IV = intravenous; RSI = rapid-sequence intubation.

Other sedatives commonly used for sedation such as benzodiazepines and neuroleptics can be problematic for a number of reasons. Respiratory depression and prolongation of the cardiac QT interval have been described with these medications.<sup>26,27</sup> Both are complications associated with unintended sudden death, and long QT syndrome has been postulated as a possible mechanism of death in ExDS.<sup>28</sup> The need for additional sedation has also been described when only benzodiazepines are used.<sup>29</sup> Since patients with ExDS are well past the levels of agitation seen in those who are simply manic, hallucinatory, belligerent, or intoxicated, controlling them often requires large doses of typical sedatives often involving more than one medication. With increasing doses or multiple medication combinations comes the increased risk of respiratory depression. This is particularly dangerous in this setting because of the respiratory drive needed to compensate for the severe underlying metabolic acidosis. Ketamine keeps protective airway reflexes intact and rarely affects respiratory drive even with increased dosages.<sup>30,31</sup> There is little danger in giving a larger dose of ketamine than is necessary to reach dissociation, as this will only prolong the sedation duration. This makes effective estimation of dosage by prehospital personnel in a dynamic and stressful situation much easier and lessens the need for absolute dosing precision.

We believe that ketamine represents an ideal sedative for use in the setting of ExDS with profound agitation. During extreme anaerobic exertion, high minute ventilation is required to buffer an acidotic condition. Chan et al. showed that physical restraint does not significantly affect ventilation after exertion.<sup>32</sup> However, physical restraint and its true effect on compensatory ventilation is difficult to study for extreme situations and it is unreasonable to physically restrain someone and allow continued exertion against the restraints. Thus, chemical restraint is necessary and needs to be reliable and effective with rapid onset, and possess an acceptable side-effect profile.

## CONCLUSION

We have presented two cases that highlight the typical clinical presentation and pathophysiology of severe ExDS. Awareness and prevention of sudden death in ExDS should be a primary concern. Management must be directed at immediate intervention, with the goal of rapid sedation to prevent further agitation, resistance, metabolic acidosis, and catecholamine surge.

The use of ketamine as a sedation agent in the prehospital control and management process appears to offer the excellent combination of rapid onset with a low side-effect profile. It can be easily administered in the prehospital environment with success. This strategy bears further study and surveillance by the pre-

hospital care community for evaluation of side effects and unintended complications.

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